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THE RESPONSES OF ANIMALS INHALING NITROGEN DIOXIDE FOR SINGLE, SHORT-TERM EXPOSURES

THEOPHILUS R. CARSON
MITCHELL J. ROSENHOLTZ, CAPTAIN
FRANK T. WILINSKI

U. S. ARMY CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES
ARMY CHEMICAL CENTER, MARYLAND

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BIOMEDICAL LABORATORY
AEROSPACE MEDICAL LABORATORY
AERONAUTICAL SYSTEMS DIVISION
AIR FORCE SYSTEMS COMMAND
UNITED STATES AIR FORCE
WRIGHT-PATTERSON AIR FORCE BASE, OHIO

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CONTRACT MONITOR: KENNETH C. BACK, PH.D.
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FOREWORD

Investigations of the responses of animals inhaling nitrogen dioxide described herein were conducted by Theophilus R. Carson, Mitchell J. Rosenholtz, and Frank T. Wilinski of the Directorate of Medical Research, U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland. They were performed under Air Force Project No. 7165, "Health Hazards of Materials and Radiation," Task No. 71836, "Evaluation and Control of Toxic Chemical Materials." The contract monitor was Dr. Kenneth C. Back, Toxic Hazards Section, Physiology Branch, Biomedical Laboratory of the Aerospace Medical Laboratory. The experiments were performed between June 22, 1960 and December 16, 1960.

The authors express their sincere appreciation to Dr. Fred W. Oberst and Dr. L. A. Sternberger for their suggestions and under whose supervision these experiments were conducted.

ABSTRACT

These experiments were designed to study the effects of NO_2 at various concentration levels below the LC50 (Lethal Concentration 50) for single, short-exposure periods to obtain concentrations causing minimal effects to animals.

Rats and rabbits were exposed to various concentrations of NO_2 for 5 to 60 minutes and the LC50's calculated. In addition, rats and dogs were exposed for single 5- to 60-minute periods to various concentrations of NO_2 below the rat LC50's. Toxic signs, pathologic changes in the lung and lung-to-body weight ratios correlated directly with the severity of exposure to NO_2. Dogs showed only mild toxic signs at concentrations causing pulmonary edema in rats. Based on lung-to-body weight ratios and pathologic changes found, the concentrations of NO_2 at which minimal effects were found were 104, 65, and 28 ppm for 5, 15, and 60 minutes, respectively.

PUBLICATION REVIEW

Jos M Quashnock

JOSEPH M. QUASHNOCK
Colonel, USAF, MC
Chief, Biomedical Laboratory
Aerospace Medical Laboratory

THE RESPONSES OF ANIMALS INHALING NITROGEN DIOXIDE FOR SINGLE, SHORT-TERM EXPOSURES

INTRODUCTION

The possibility of men being exposed to high concentrations of nitrogen dioxide ($NO_2 \rightleftharpoons N_2O_4$) for short periods of time has become considerably greater because some advanced missiles require storage of large quantities of this material. This hazard created the need for additional toxicological information designed to aid in estimating a safe concentration of NO_2 in man for single, short exposures.

Others are interested in the toxicity of the oxides of nitrogen because of the possibility of accidental exposures under various circumstances. Although many of these exposures were for short periods of time, little is known about the exposure concentrations. Some of the findings in people exposed to the oxides of nitrogen as reported by various investigators (1,2,4,9,12,14,15) are pulmonary edema, pneumonia, bronchiolitis obliterans, and death. Animal studies for short, single exposure periods reported by others (7,10,13) show that NO_2 is primarily a respiratory irritant which, in sufficient concentration, causes pulmonary edema, pneumonia, and death. However, the differences in approach in these experiments makes it difficult to equate the concentrations of NO_2 at which these effects occur. In addition, these animals experiments were not designed to determine the effects that NO_2 causes at concentrations below the LC50 (Lethal Concentration 50). Therefore, experiments were designed to study the effects of NO_2 at progressively lowered concentrations for single, short exposure periods to obtain concentrations causing minimal or no effects to animals.

This report describes the responses of animals occurring from single 5- to 60-minute NO_2 exposures at concentrations in the LC50 range and at various concentrations below the LC50.

METHODS

A. Techniques of Exposures

1. Dispersion

NO_2 was metered from a cylinder through an expansion flask (1000 ml) and a manometer containing silicone oil and into a 400 liter dynamic gassing chamber. The NO_2 cylinder*, expansion flask, and manometer

*Purchased from the Matheson Company, Inc., E. Rutherford, New Jersey.

were maintained at 31°C in a constant temperature box. The chamber was equipped with a sliding carriage to facilitate the short-term exposures.

2. Collection and Analysis of Chamber Air Samples

Chamber air samples were pulled by vacuum into calibrated gas sampling bottles varying from 50 to 1000 ml depending upon the concentration of the chamber air sampled. The sampling rate varied from 50 to 500 ml depending upon the size of the sampling bottle. The gas bottles were then cooled in a dry ice-acetone bath and the absorbing reagent was introduced. The samples were analyzed colorimetrically by the method described by Saltzman (17). For the five-minute exposures a sample was taken before and during exposure. For all other exposure times, two to three samples were taken during exposure. There was very little variation between the several samples taken at various times during the exposures. The concentrations are expressed as ppm of NO_2.

B. Exposure and Observation of Animals

Rats and rabbits were exposed for single 5- to 60-minute periods to various concentrations of NO_2. Mortality and toxic signs were observed in these animals during and after exposure. These exposures were for LC50 determinations and are called high level exposures.

1. High Level NO_2 Exposures

Young male rats (100 to 120 gm) were exposed in groups of 10 to various concentrations of NO_2 for single 5-, 15-, 30-, and 60-minute periods. The LC50s were calculated for each exposure time by the method of Bliss (5). The survivors were weighed and observed for 21 days after exposure.

Rabbits (2.2 to 2.7 kg) in groups of five were exposed for 15 minutes to various concentrations of NO_2 and the LC50s were calculated. The survivors were weighed and observed daily for 7 days after exposure and were sacrificed 21, 42, and 90 days after exposure for pathologic studies.

2. Low Levels NO_2 Exposures

Rats were exposed to NO_2 at different concentrations below the LC50s for each of three exposure periods. Young male rats (100 to 120 gm) were exposed in groups of 30 for 5, 15, and 60 minutes to concentrations approximating 50, 25, 15, and 5 percent of each of the LC50s. Exposed rats for all concentrations and a group of controls were sacrificed in groups of five at 4, 24, and 48 hours; 7, 21, and 42 days after exposure. Toxic signs, kidney to body and lung to body weight ratios, and pathologic changes were used as criteria for evaluating the effects of each exposure. Kidney to body weight ratios were determined only at concentrations of 50 and 25 percent of the LC50s.

After it was found that the concentrations causing minimal effects in rats occurred at 25 percent of the LC50s, dogs were exposed in groups of two to concentrations of NO_2 approximating 50 and 25 percent of the LC50s for rats for 5, 15, and 60 minutes. These exposures were for the purpose of observing the response of a larger species at what was believed to be the threshold concentrations for rats. The dogs were observed for toxic signs. Blood platelet counts and hematocrit (18) were determined for each exposure time. The hematologic studies were performed at 4, 24, 48, and 72 hours after exposure. One dog was sacrificed at 21 days after exposure and the other at 42 days after exposure.

C. Pathology

Rats and rabbits from the LC50 exposures were examined for gross pathologic changes. The lungs received particular attention. Microscopic examinations for lung lesions were made only on rabbits. Organs from animals receiving NO_2 at concentrations below the LC50 level were examined for both macro and microscopic changes. These organs included lung, liver, kidney, spleen, heart, eyes, and gastrointestinal tract. Thiopental sodium was used, interperitoneally in rats and rabbits, and intravenously in dogs, to sacrifice the animals. The rats from which kidneys and lungs were taken to determine organ-body weight ratios were sacrificed following light anesthesia. A group of control animals for each exposure group was sacrificed under the same conditions. All tissues for microscopic studies were fixed in 10 percent Formalin and stained with hematoxylin and eosin.

RESULTS

A. Exposure and Observation of Animals

The responses of animals exposed to high and low concentrations of NO_2 are detailed in the following sections.

1. High Level Exposures

The 5-, 15-, 30-, and 60-minute LC50 values for rats and the 15-minute LC50 value for rabbits with 19/20 confidence limits and slopes of the dose-response curves with their standard errors are shown in Table 1. The toxic signs of the animals exposed to NO_2 were about the same for both species: This included severe respiratory distress, eye irritation as shown by reddened conjunctiva, 10 to 15 percent body weight supression lasting for two days, and death. The times of death varied from 30 minutes to three days after exposure. Animals surviving three days after exposure appeared to have recovered from the respiratory distress and eye irritation.

TABLE 1

LC50 VALUES FOR ANIMALS EXPOSED TO NO_2

Exposure Time	LC50	Species	19/20 Confidence Limits	Slope	Standard Error of the Slope
min	ppm		ppm		
5	416	Rats	376-461	9.5	± 4.2
15	201	Rats	191-212	15.3	± 4.1
15	315	Rabbits	290-342	13.1	± 5.9
30	162	Rats	152-169	20.7	± 5.1
60	115	Rats	113-117	43.3	± 12.8

2. Low Level NO_2 Exposures

The exposure sequences to various low level concentrations of NO_2 including the exposure times, species used, and the percentages of the LC50s at which the experiments were conducted are summarized in Table 2.

TABLE 2

EXPOSURE SEQUENCES TO LOW LEVELS OF NO_2

Exposure Time	Species	Concn of NO_2 Approximating Percentages of the LC50s for Rats			
		50%	25%	15%	5%
min		ppm	ppm	ppm	ppm
5	Rats	190	104	74	27
5	Dogs	164	125	Not done	Not done
15	Rats	90	65	33	18
15	Dogs	85	52	Not done	Not done
60	Rats	72	28	11	Not done
60	Dogs	53	39	Not done	Not done

a. Response of Animals Exposed to 50 Percent of the LC50s

The toxic signs in rats were about the same at these concentration levels regardless of the exposure time. The toxic signs were severe respiratory distress, lasting about two days, and reddened conjunctiva but no deaths. The lung to body weight ratios usually showed a significant increase during the first 48 hours after exposure and in most cases returned to normal by the seventh day. The growth rate and kidney to body weight ratio were not affected at these concentrations.

The dogs showed some respiratory distress during exposure which lasted, in most cases, from only a few hours to two days. The respiratory distress was indicated by either hyperventilation which subsided within 60 minutes after exposure or by a mild cough which subsided in about two days after exposure. On removal from the chamber the dogs showed eye irritation as indicated by reddened conjunctiva which cleared up within a day or two after exposure. No changes were noted in hematocrit or blood platelet count.

b. Response of Animals to 25 Percent of the LC50s

Rats showed some respiratory distress during exposure which subsided within an hour after exposure. The lung to body weight ratio showed a significant increase above controls which usually lasted for 48 hours. The growth rate and kidney to body weight ratio were not different from control values.

At this concentration level (25% of rat LC50) dogs showed only a little discomfort but no marked respiratory distress, no eye irritation, and no changes in hematocrit or blood platelet count.

c. Responses of Rats to 15 and 5 Percent of the LC50s

No toxic signs or significant increases in lung to body weight ratios were seen in animals exposed to these concentration levels.

B. Pathology

1. High Level NO_2 Exposures (LC50s)

The gross pathology in rats showed many darkened areas about the surface of the lungs and in some instances purulent nodules involving entire lungs of some of the surviving rats were seen. Rabbits showed some darkened areas about the surface of the lungs but no purulent nodules were seen.

Microscopic studies of rabbits surviving the LC50 exposure showed lesions in the lungs when sacrificed 7 and 21 days after exposure. These lesions were featured by focal accumulation of intra-alveolar macrophages, some proliferation of the alveolar lining epithelium, and varying

amounts of inflammatory cells. No definite evidence of such lesions were noted at 42 and 90 days after exposure.

2. Low Level NO_2 Exposures

a. 50 Percent of LC50s for Rats

The gross pathologic findings showed many darkened areas about the surface of the lungs during the first seven days after exposure. At 21 and 42 days after exposure some rats showed areas appearing as pneumonia. Microscopic studies in rats showed apparent pulmonary edema during the first 48 hours after exposure. The pattern was significantly different from the controls. Examination for more complex pulmonary parenchymal lesions was complicated by the presence of chronic murine pneumonia. This pneumonitic process became more prevalent and more extensive as the post exposure time increased. There was some suggestion that exposure to NO_2 at this concentration level increased the likelihood of seeing chronic murine pneumonia. There were no microscopic changes in the eyes. Other organs studied were within the normal range.

Studies of dogs at this level (50% of rats LC50s) showed no definite gross or microscopic lesions which were not present in controls.

b. 25 Percent of LC50s for Rats

There were no gross pathologic lesions noted in rats or dogs. However, some of the rats examined microscopically at 24 and 48 hours after exposure manifested apparent pulmonary edema. Chronic murine pneumonia also was present in some rats. No histological changes were seen in the eyes or other organs studied, except the lungs. In the exposed dogs no gross or histologic changes were seen in the lungs that were different from the controls.

c. 15 to 5 Percent of LC50s for Rats

None of the rats studied showed changes not present in controls.

DISCUSSION

The toxic effects of NO_2 seen in these short-term exposures were primarily irritation of the eyes and the pulmonary tract. The pulmonary damage is by far the most dangerous effect caused by this gas. Other investigators (8,9,10) found in single, short exposures comparable to ours, that the damage caused by the oxides of nitrogen (probably $NO_2 \rightleftharpoons N_2O_4$) is primarily on the respiratory tract. However, there is disagreement as to the concentrations at which severe effects and death occur in animals. Gray (8) has pointed out that these differences are probably due to variation in analytical procedures

for NO_2 and in species, sex, and age of animals exposed. In our experiments the slopes of the dose-response curves are similar to those at corresponding exposure times reported by Gray et al. (7), but our LC50s are about one-half of those reported by him. The male rats used in our exposures weighed from 100 to 120 grams as compared to 260- to 360-gram rats used by Gray. It has been shown by others (3,11) that younger rats are more susceptible to respiratory irritants than older ones.

Toxic signs, lung to body weight ratios and pathologic changes in the lungs correlated with each other, and each of the three responses decreased in severity as the concentrations were lowered. NO_2 produced observable changes in all criteria at approximately equal dose levels. However, lung to body weight ratios provided the most quantitative and objective indication of NO_2 action on the lungs. Since this is true, it seems logical that lung to body weight ratios may be used as a reliable index of the degree of exposure to NO_2. With another respiratory irritant, cobalt hydrocarbonyl, Palmes et al. (16) showed that the lung to body weight ratios are a useful criterion to evaluate the degree of respiratory damage.

A factor to consider in the lung to body weight ratios based on results from our exposures is that beyond the first seven days after exposure chronic murine pneumonia in rats complicated interpretation of the ratios and the pathologic changes in the lungs. However, the importance of this complication may be minimal, since the clinical signs and lung to body weight ratios indicated that the pulmonary edema usually subsided within 48 hours after exposure. Although the pneumonia in the control rats complicated the picture, the lungs of exposed rats indicated a higher incidence of this pneumonic condition.

Dogs were exposed to the threshold concentrations for the rat, and the toxic signs and pathologic changes indicate that they tolerated these exposures better than the rats. In addition, no changes were noted in blood platelet counts or hematocrits of the dogs. However, Fleming (6) exposed dogs between 2 1/2 and 7 minutes to concentrations of the oxides of nitrogen comparable to our exposures and found significant increases in blood platelet counts. He suggested that the increase in platelet count could be used as an index of the degree of edema resulting from exposure. Since we were not able to demonstrate blood platelet count increases, nor edema at similar concentrations reported by him, the differences in findings may be due to the sources of gas and to analytical procedures. He generated his gas by the action of sulfuric acid on known amounts of sodium nitrate, whereas we used pure NO_2 gas. He also analyzed for both nitrites and nitrates. Our analytical method analyzed only for nitrites and was adjusted for the portion of the gas shown experimentally to form nitrates. He also collected his chamber air samples with three absorbers in series containing 0.1 normal sodium hydroxide. In preliminary trials, we were unable to collect all of the chamber concentration using pure NO_2 gas with three bubblers containing 0.1 normal sodium hydroxide or the absorbing reagent, even at very slow rates (50 ml/min). This fact was shown when compared with chamber air samples collected in gas sampling bottles.

Therefore, Fleming's concentrations could have been considerably higher than those reported, or could be due to the impurities of other oxides of nitrogen which had a different action. However, he did find that rats were very sensitive to the oxides of nitrogen and this is in agreement with our findings.

The effects of NO_2 on lung to body weight ratios of rats at percentages of the LC50s with time are summarized in figure 1. The area between lines AB and CD is the area causing severe lung damage and probable death in rats. In the area between lines CD and EF one can expect marked edema during the first 48 hours after exposure. Below line EF one can expect borderline or no changes in the lungs of rats. Therefore, 25 percent of the LC50s seems to be the threshold concentrations for rats and are 104, 65, and 28 ppm for 5, 15, and 60 minutes exposure, respectively.

SUMMARY

Rats and dogs were exposed for single 5- to 60-minute periods to various concentrations of NO_2. Lung to body weight ratios of rats correlated directly with the severity of exposure to NO_2. The kidney to body weight ratios of rats, the hematocrits, and blood platelet counts of dogs were of little or no value in evaluating the severity of NO_2 exposures. Dogs showed only mild toxic signs at NO_2 concentrations which caused pulmonary edema in rats. Based on lung to body weight ratios of rats and the pathological changes found, the concentrations of NO_2 at which no effects were found were 104, 65, and 28 ppm for 5, 15, and 60 minutes, respectively.

From this information, estimates may be made for safe exposure concentrations of NO_2 to man at various exposure times.

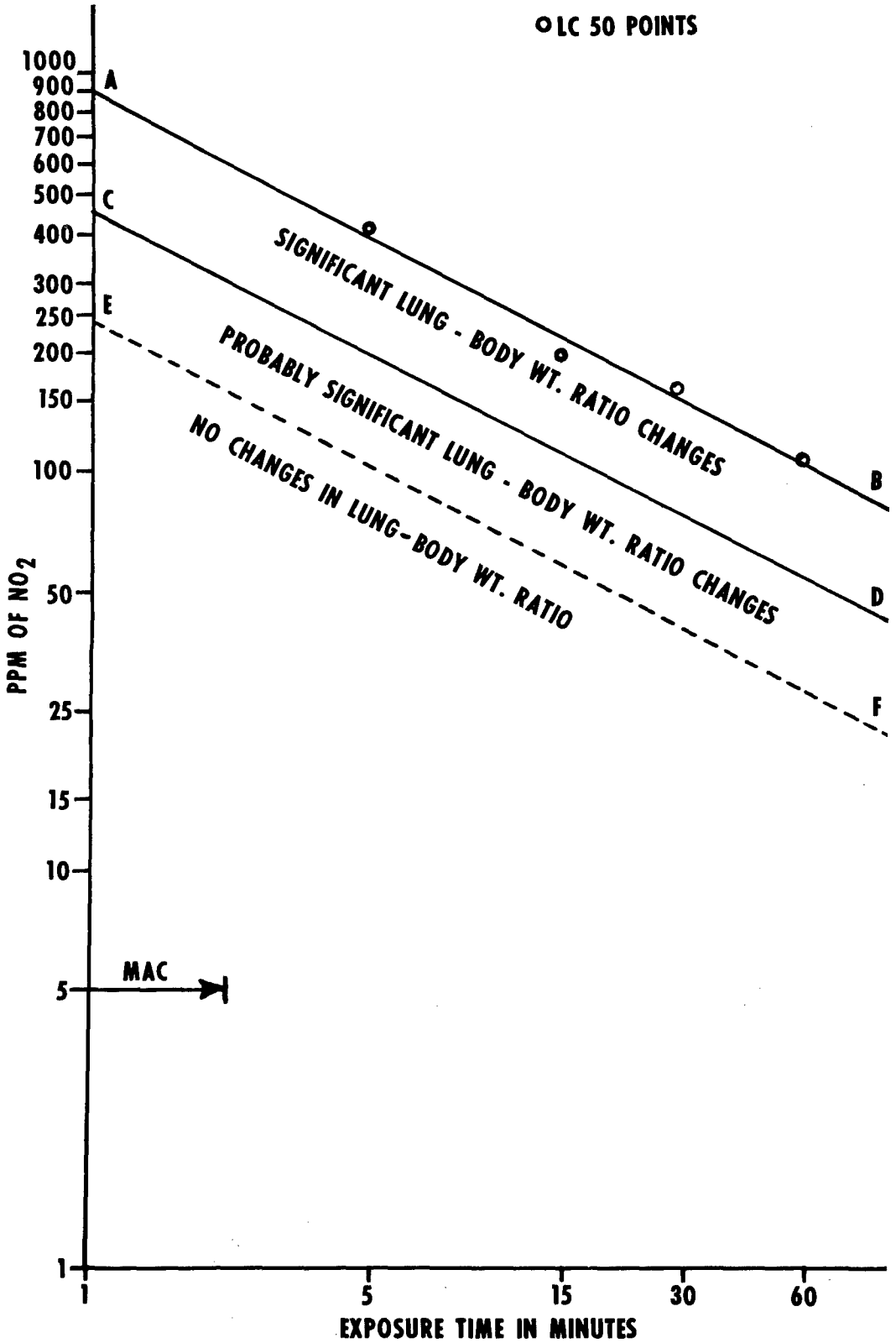

Figure 1. Response of Rats to NO_2
Lung - Body Wt. Ratio Changes at Percentages of LC50

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U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland

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I. Carson, T. R.
II. Rosenholtz, M. J.
III. Wilinski, F. T.
IV. Aeronautical Systems Division, Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio
V. MIPR (33-616) 60-32

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